

## **Effect of the direct oral anticoagulants rivaroxaban and apixaban on the disposition of calcineurin inhibitors in transplant recipients**

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**Author contributions**

TV researched the data and wrote the article. DK and TV designed the study. IS, PA, JM, JVC, and RV supplied data and reviewed the article.

## **Disclosures**

DK and JM have served as consultants to Astellas Pharma and have been on the speaker's bureau for Astellas Pharma. DK, JM, and JVC have received research funding from Astellas Pharma. The other authors report no relevant conflict of interest.

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## **Abbreviations**

C0/D	Dose-corrected trough concentration
CNI	Calcineurin inhibitor
CYP3A	Cytochrome P450 3A4 and 3A5
DDI	Drug–drug interaction
DOAC	Direct oral anticoagulant
P-gp	P-glycoprotein
VKA	Vitamin K antagonist

## **Abstract**

**Background.** Calcineurin inhibitors (CNIs) and direct oral anticoagulants (DOACs) share certain metabolic pathways, but whether DOACs influence CNI exposure has not been assessed.

Methods. A single-center retrospective analysis was performed including 39 organ recipients treated with the combination of a CNI and rivaroxaban (n = 29) or apixaban (n = 10). Dose-corrected CNI trough concentrations (C0/D) during 200 days before and after DOAC initiation were recorded (n = 261), together with covariates known to influence CNI disposition such as steroid dose and hematocrit. The average C0/D before and during DOAC therapy was compared using paired samples t-test. Multivariable mixed models were constructed to estimate the effect of DOAC and other predictors on C0/D at each time point.

Results. Group average C0/D was not significantly different before and during DOAC therapy for any CNI–DOAC combination ( $p = 0.089$ – $0.761$ ), although C0/D changed  $>20\%$  in 19/39 patients (13 increases, 6 decreases). In multivariable analysis, independent predictors of tacrolimus C0/D were methylprednisolone dose ( $p = 0.039$ ) and concomitant use of a CYP3A inhibitor ( $p = 0.007$ ). The subgroup analysis per DOAC showed a limited but significant effect of rivaroxaban on tacrolimus C0/D (9.2% increase,  $p = 0.042$ ). Independent predictors of ciclosporin C0/D were age ( $p = 0.018$ ) and use of any DOAC (12.1% increase,  $p = 0.020$ ).

Conclusions. Apixaban, and particularly rivaroxaban, may cause a limited ( $<20\%$ ) increase in CNI trough concentration, an effect that is unlikely to trigger a dose change. It may be prudent to perform an

additional CNI trough concentration measurement five to seven days after DOAC initiation, but pre-emptive CNI dose changes are not warranted based on these observations.

### **Keywords**

Tacrolimus; ciclosporin; apixaban; rivaroxaban; drug interaction

### **Introduction**

A significant proportion of transplant recipients requires temporary or long-term systemic anticoagulation, mainly as a result of atrial fibrillation, deep venous thrombosis, or pulmonary embolism.<sup>1–3</sup> Vitamin K antagonists (VKAs) have historically been the standard of care for long-term anticoagulation in solid organ recipients, similar to the general population. Over the last years, however, several direct oral anticoagulants (DOACs) including dabigatran, rivaroxaban, and apixaban have become available. These are an attractive option because they are efficient, safe, and do not need to be systematically monitored.<sup>4,5</sup> However, clinicians may be reluctant to use them in transplant recipients because data regarding their use in this specific population are scarce. Furthermore, DOACs and the calcineurin inhibitors (CNIs) tacrolimus and ciclosporin share certain metabolic pathways that could raise concerns over potential bi-directional drug interactions.

The CNIs tacrolimus and ciclosporin are substrates of the cytochrome P450 iso-enzymes 3A4 and 3A5 (collectively referred to as CYP3A) and the efflux pump P-glycoprotein (P-gp or ATP-binding cassette subfamily B member 1 (ABCB1), encoded by the multidrug-resistance-1 gene (*MDR1*)). CYP3A and P-gp are present in the intestine (where they limit oral bioavailability) and the liver (where CYP3A metabolizes the great majority of circulating CNI and P-gp facilitates biliary excretion of the CNI and its metabolites).<sup>6</sup> Inhibitors of CYP3A and/or P-gp will result in an increased exposure to CNIs, commonly assessed by the measurement of blood concentration (either as area under the time curve (AUC) or as trough concentration measurement). Tacrolimus and ciclosporin are themselves *in vitro* inhibitors of CYP3A and P-gp, although this is probably only clinically relevant for ciclosporin, which is a potent P-gp inhibitor and moderate CYP3A4 inhibitor.<sup>7,8</sup> All three abovementioned DOACs are also substrates for P-gp, but the contribution of CYP enzymes to their disposition is more variable. Dabigatran is not metabolized by any CYP450 enzyme *in vitro*. CYP3A4 and CYP2J2 account for approximately 18% and 14% of total rivaroxaban elimination,<sup>9</sup> whereas apixaban is mainly metabolized by CYP3A.<sup>10</sup> Some of the most studied combined P-gp/CYP3A inhibitors include ketoconazole and verapamil, which increase the exposure of all DOACs. There is no evidence that DOACs exert an effect on P-gp or

CYP3A based on *in vitro* data and/or studies in limited numbers of healthy volunteers (in the case of rivaroxaban).<sup>11</sup> Whether this remains true in a clinical context has not been assessed. The aim of this study, therefore, was to evaluate whether DOAC therapy influences CNI exposure in transplant recipients to a clinically relevant degree.

## **Materials and methods**

### **Study design and population**

This was a single-center retrospective cohort analysis. The electronic hospital pharmacy billing and prescription records were queried to identify transplant patients who had been prescribed a CNI (tacrolimus [Prograf® or Advagraf®, Astellas Pharma, London, UK] or ciclosporin [Neoral®, Novartis, Basel, Switzerland]) together with a DOAC (dabigatran [Pradaxa®, Boehringer Ingelheim, Ingelheim, Germany], rivaroxaban [Xarelto®, Bayer, Leverkusen, Germany], or apixaban [Eliquis®, Bristol-Myers Squibb, New York, US]). Inclusion criteria were (1) concomitant administration of a CNI and a DOAC during at least seven days, (2) availability of at least two CNI trough concentrations before and at least one trough concentration during (and at least three days after the initiation of) concomitant DOAC therapy. Exclusion criteria were (1) less than seven days' concomitant administration of CNI and DOAC and (2) initiation of a CYP3A

inhibitor/inducer around the time DOAC initiation so that the individual effect of the DOAC could not be determined. CYP3A inhibitors/inducers were classified as moderate or strong based on the Food and Drug Administration classification of their in vivo inhibitory/inductive potency.<sup>12</sup> In- and outpatient CNI trough concentrations were registered between 200 days before and 200 days after DOAC initiation. All trough concentrations were corrected for CNI daily dose (using the dose taken the day before trough concentration measurement). Hematocrit, methylprednisolone dose, use of concomitant CYP3A inhibitor/inducer, and weight were registered at the time of every trough concentration determination. Changes in CNI C<sub>0</sub>/D >20% (increase or decrease) were (arbitrarily) considered significant, as changes <20% are unlikely to result in a dose change by the treating physician. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula.<sup>13</sup> Hepatic dysfunction was defined as serum alanine aminotransferase more than three times the upper limit of normal, total bilirubin >2 mg/dl or known hepatic cirrhosis. Adverse events (such as bleeding) were identified by chart review. As this was a retrospective analysis of anonymously reported, routinely collected clinical information, an informed consent and approval by the ethics committee were not pursued.



## Statistical analysis

Data are presented as mean  $\pm$  standard deviation except when stated otherwise. Normality was tested using the Shapiro-Wilk test. C0/D was not normally distributed and log-transformed for analysis [ $\ln(\text{C0/D}+1)$ ]. C0/D ratios of tacrolimus and ciclosporin were always analyzed separately. CNI C0/D ratios before and during DOAC therapy were compared in two ways. First, average C0/D in the last 100 days before and the first 100 days after the initiation was calculated and compared using paired samples t-test. Analyses were repeated using the average of the last three C0/D ratios before and the first three C0/D ratios after DOAC initiation, which yielded virtually identical results and is not further reported. Second, all available C0/D ratios were entered in a linear mixed model to take into account the correlation between C0/D ratios in each patient and to allow modeling of time-related C0/D variability. A linear mixed model with random intercepts and a first-order autoregressive covariance structure was used to estimate the effect of covariates on CNI C0/D. The following variables were considered as possible fixed effect predictors of C0/D: gender, age, methylprednisolone dose, use of DOAC, type of DOAC, DOAC dose, use of concomitant CYP3A inhibitor, years post-transplantation, hepatic dysfunction, eGFR, and hematocrit. Weight was not considered as a predictor because it was only sporadically registered. Calculation of estimates was based on

the restricted maximum likelihoods. In the final mixed model, we only included those terms that were statistically significant using F test and improved the model according to Akaike's information criterion (AIC). Intra-patient variability of all available C0/D ratios in the 100 days before DOAC initiation was calculated as coefficient of variability (standard deviation/mean CNI C0/D)  $\times$  100%. Intra-patient variability could only be calculated for 30 patients, as 9 patients did not have sufficient C0/D ratios to calculate a standard deviation. A two-sided p-value  $<0.05$  was considered statistically significant. For collinearity diagnostics, a variance inflation factor of  $>5$  was considered indicative of multicollinearity. All analyses were performed using IBM SPSS Statistics version 22 (IBM, NY, USA). Figures were generated using Graphpad Prism version 6 (San Diego, CA, USA).

## **Results**

### **Study population**

Sixty-seven patients were identified that had been concomitantly treated with a CNI and a DOAC between January 2012 and May 2016. Of these, 28 were excluded because the DOAC had been given less than 14 days ( $n = 4$ ), insufficient CNI trough concentrations were available ( $n = 20$ ), or a potent CYP3A inhibitor was initiated together with the DOAC and not stopped before DOAC cessation ( $n = 3$ ). Only one

patient was treated with dabigatran and was not included in the analysis. Demographics of the final study population are presented in Table 1. Of 29 tacrolimus-treated patients, 22 received rivaroxaban (total of 149 trough concentrations of which 77 were during co-treatment), and 7 apixaban (43 trough concentrations, 18 during co-treatment). Of 10 ciclosporin-treated patients, 7 received rivaroxaban (43 trough concentrations, 20 during co-treatment) and 3 received apixaban (26 trough concentrations, 14 during co-treatment). Four patients were treated with a moderately strong CYP3A inhibitor at the time of at least one of the included CNI trough concentrations: three with amiodarone and one with fluconazole. No other CYP3A and/or P-gp inhibitors and inducers were registered. Hepatic dysfunction was present in one patient.

### **C0/D before and during DOAC therapy**

Average C0/D was not significantly different before and during DOAC therapy for any CNI–DOAC combination ( $p = 0.089–0.761$ ) as shown in Figure 1. Because stable group averages may obscure changes in C0/D that occur in individual patients, the latter are plotted in Figure 2. Significant ( $>20\%$ ) changes in C0/D occurred in 13/22 patients in the tacrolimus–rivaroxaban group (9 increases, 4 decreases), 3/9 in the tacrolimus–apixaban group (1 increase, 2 decreases), 2/7 in the

ciclosporin–rivaroxaban group (2 increases), and 1/3 in the ciclosporin–apixaban group (increase). In each of these subgroups of patients in which C0/D significantly changed, average CNI dose was not significantly different after DOAC initiation (data not shown). Only a trend was noted in tacrolimus–rivaroxaban co-treated patients in whom C0/D increased after rivaroxaban initiation ( $n = 9$ ), where the average tacrolimus dose was  $1.12 \pm 1.45$  mg/dl lower after rivaroxaban initiation ( $p = 0.066$ ). This indicates that, on average, physicians accepted the alteration in exposure and did not change CNI dose. For clarification, the three subgroups of C0/D evolution (stable, increase, and decrease) in tacrolimus–rivaroxaban co-treated patients are plotted separately in Figure 3. The ratio between the average C0/D before and after DOAC initiation was positively correlated with the degree of intra-patient variability in pre-DOAC C0/D ratios (Pearson correlation coefficient 0.445,  $p = 0.014$ ), indicating that patients with high baseline variability in CNI exposure were also more likely to display a significant change in exposure between the pre- and post-DOAC phases.

### **Determinants of C0/D over time**

As the abovementioned comparison of C0/D values before and during DOAC therapy does not take into account other covariates known to influence CNI pharmacokinetics (patient age, time after

transplantation, hematocrit [particularly for tacrolimus], steroid dose, concomitant use of other CYP3A inhibitors/inducers and hepatic dysfunction)<sup>6</sup> or time-related variability and correlations between C0/D ratios in individual patients, a linear mixed model analysis was performed. The results of this analysis are presented in Table 2. Significant predictors of C0/D in tacrolimus-treated patients were the intercept (indicating significant differences between patients), methylprednisolone dose, and use of concomitant CYP3A inhibitor, but not DOAC use. Figure 4 is a scatterplot of tacrolimus C0/D by methylprednisolone dose, which further illustrates their significant correlation. In ciclosporin-treated patients, predictors were age and DOAC use. The estimated effect of DOAC use in ciclosporin-treated patients was a 12.1% (95% CI, 2.1-22.2%) increase in C0/D.

In the abovementioned analysis, rivaroxaban and apixaban were grouped into one predictor variable; separate analyses for each combination of CNI and DOAC are presented in Tables S1-2 <http://links.lww.com/TDM/A176>. Here, DOAC use was a significant predictor of C0/D in the tacrolimus–rivaroxaban group and borderline significant in the ciclosporin–rivaroxaban group (estimated effects 0.092 (0.003-0.180),  $p = 0.042$  and 0.127 (0.010-0.265),  $p = 0.068$ ; respectively). This corresponds with a 9.2–12.7% estimated increase in C0/D related to rivaroxaban use after correction for steroid dose, time,

and concomitant use of other CYP3A inhibitors. Hematocrit was not predictive of C0/D in this analysis.

## **Safety**

The average follow-up period under concomitant CNI–DOAC therapy was 34 months, during which time bleeding events were registered in two patients. One patient with a suprapubic catheter on tacrolimus–apixaban had a single episode of macroscopic hematuria that remained unexplained. One patient on tacrolimus–rivaroxaban had repetitive episodes of macroscopic hematuria related to bladder lithiasis, for which she received endoscopic treatment. DOAC treatment was continued in both patients.

## **Discussion**

This study indicates a possible effect of the DOACs rivaroxaban and apixaban on CNI disposition that is, however, unlikely to be clinically relevant. Group average C0/D ratios were similar before and during DOAC therapy. Although C0/D evolution differed considerably between individual patients, there was no clear pattern. Both increased CNI C0/D (which would occur if DOACs inhibited CYP3A and/or P-gp) and decreased CNI C0/D (which would occur if DOACs induced CYP3A and/or P-gp) occurred. There was a strong positive correlation between

pre-DOAC intra-patient variability in CNI exposure and the change in CNI exposure after DOAC initiation. This suggests that a strongly altered C0/D after DOAC initiation is often simply a reflection of high pre-existing time-related variability in exposure in that patient, whatever the underlying cause. Finally, after correcting for variables known to influence CNI disposition in mixed model analysis, only rivaroxaban was associated with a 9.2% increase in C0/D of tacrolimus ( $p = 0.042$ ) and a 12.7% increase in C0/D of ciclosporin (not significant at  $p = 0.068$ ). We note that, for a stable dose, a 12.7% change in C0/D also implies a 12.7% change in trough concentration. This is unlikely to be clinically relevant. Most changes in drug exposure of  $<20\%$  are considered to be well within the range of biological variability and, even in the case of CNIs, will generally not justify a dose change. However, it is important to note that susceptibility to drug–drug interactions (DDIs) varies considerably between individuals. For example, ciclosporin increased repaglinide AUC 2.4-fold on average in healthy volunteers, but the range was 1.2- to 5.3-fold and was partly genetically determined.<sup>14</sup> The absence of a systematic effect does not exclude an interaction in individual patients, which is why it does not suffice to compare group average trough concentrations or C0/D ratios. For the same reason, studies using limited numbers of healthy volunteers can be used to confidently exclude a major interaction but do not obviate the need for

post marketing DDI surveillance. Some patients might still be predisposed to engage in moderate interactions, which may necessitate dose changes for drugs with a narrow therapeutic index such as CNIs. In the case of CNIs and DOACs, this study is in line with preclinical data<sup>10,11</sup> suggesting that if DOACs have an effect on CNI disposition, it will likely be irrelevant in most (but not necessarily all) patients.

This study has limitations. First, it is a retrospective analysis of clinical data from a relatively limited number of patients that received different types of transplants. Several potential sources of variability (e.g., noncompliance, diarrhea) were not systematically registered and could therefore not be accounted for. On the other hand, the clinical factors that influence CNI disposition in organ recipients are well characterized and most were corrected for in the mixed model analysis. Although this is a thorough way of analyzing longitudinal clinical data, it cannot circumvent the inherent limitations of the dataset and must be considered complementary to controlled pharmacokinetic studies (generally performed in healthy volunteers). Second, it would have been interesting to include genotype information, as there is some evidence that certain genetic polymorphisms (e.g., CYP3A5\*1) may diminish the impact of CYP3A inhibitors on tacrolimus disposition.<sup>15,16</sup> Third, this study could not address the potential effect of CNIs on DOACs, since DOAC trough concentration monitoring was performed only sporadically. As



ciclosporin is a combined inhibitor of CYP3A and P-gp, it is expected to strongly increase the exposure to all three major DOACs resulting in an increased risk of bleeding, as has been demonstrated for rivaroxaban.<sup>17</sup> Finally, for C<sub>0</sub>/D to be a valid reflection of dose requirement, pharmacokinetic steady state has to be assumed. This may not have been the case for all collected values if, for example, doses had been very recently changed. However, the same is true for trough concentrations that correlate best with drug exposure in steady-state conditions and will also vary as a result of dose changes, whereas C<sub>0</sub>/D does not. AUC's are the preferred way to assess changes in exposure but were not available. Furthermore, tacrolimus AUC correlates well with C<sub>0</sub> ( $r = 0.83-0.94$ ).<sup>18</sup>

## **Conclusion**

In conclusion, rivaroxaban and apixaban do not seem to have a clinically relevant effect on CNI disposition in organ recipients. It may be prudent to perform an additional CNI trough concentration measurement five to seven days after DOAC initiation in order to quickly detect the individual patient suffering from significant DOAC-induced changes in CNI exposure. Preemptive CNI dose changes are not warranted based on these results.

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## **Figure legends**

### **Figure 1**

Average calcineurin inhibitor dose-corrected trough concentrations before and during therapy with oral anticoagulants

C0/D, dose-corrected trough concentration; DOAC, direct oral anticoagulant

### **Figure 2**

Average calcineurin inhibitor dose-corrected trough concentrations before and during therapy with oral anticoagulants, individual patient values.

C0/D, dose-corrected trough concentration

### **Figure 3**

Average tacrolimus dose-corrected trough concentrations before and during therapy with rivaroxaban, by category.

C0/D, dose-corrected trough concentration

### **Figure 4**

Scatterplot of all tacrolimus dose-corrected trough concentrations by methylprednisolone dose.

C0/D, dose-corrected trough concentration

Table 1. Patient characteristics

Characteristic	Value
Type of transplant (n)	
Kidney	18
Lung	13
Kidney + lung	2
Heart	5
Allogenic stem cell	1
Gender (male/female)	22/17
Age (years) <sup>a</sup>	63.8 ± 12.8
Caucasian ethnicity	37 (95%)
Time after transplant (years) <sup>a</sup>	9.1 ± 9.5
Calcineurin inhibitor (n)	
Tacrolimus	29
Cyclosporine	10
Oral anticoagulant	
Rivaroxaban	29
Apixaban	10
Other immunosuppressants (n)	
Mycophenolate mofetil	25
Azathioprine	5
Methylprednisolone	28
Methylprednisolone dose (mg/day) <sup>b</sup>	
Average	5.9 ± 7.7
Range	0–48
Concomitant use of CYP3A inhibitor (n)	4
Hematocrit (%) <sup>b</sup>	37.6 ± 5.4
Number of available CNI trough concentrations per	6.7 ± 1.8
Trough concentration (ng/ml) <sup>b</sup>	
Tacrolimus	9.5 ± 3.1
Ciclosporin	105.0 ± 32.6
C0/D ratio (ng/ml/mg) <sup>b</sup>	
Tacrolimus	2.5 ± 1.3
Ciclosporin	0.9 ± 0.4

<sup>a</sup>At the initiation of oral anticoagulant<sup>b</sup>Considering all available values at all time points  
C0/D, dose-corrected trough concentration

Table 2. Multivariable mixed model estimates for fixed effect predictors of calcineurin inhibitor dose-corrected trough concentrations

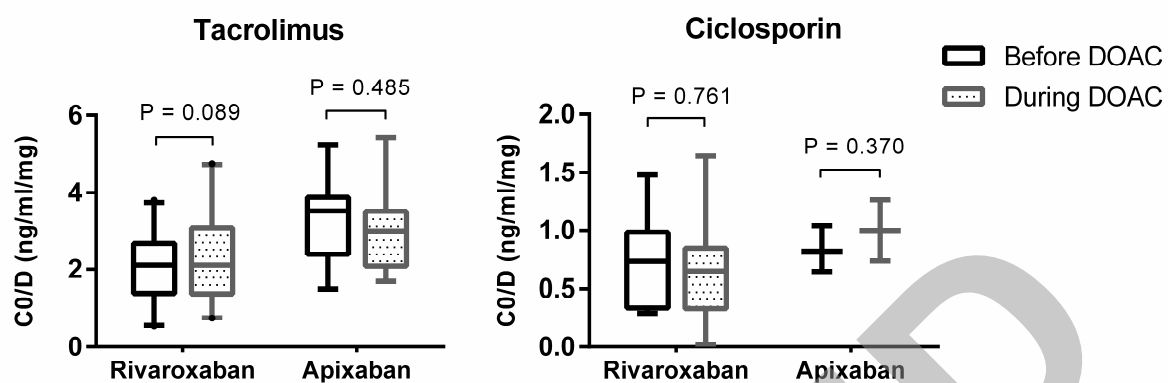
Parameter	Tacrolimus			Ciclosporin		
	Estimated effect	95% CI	p	Estimated effect	95% CI	p
Intercept	1.452	1.236-1.669	<0.001 <sup>a</sup>	-	-	0.925 <sup>a</sup>
Methylprednisolone dose (mg)	-0.007	-0.145-0.001	0.039 <sup>a</sup>	-	-	0.130
Concomitant CYP3A inhibitor use	0.264	0.075-0.452	0.007 <sup>a</sup>	-	-	- <sup>b</sup>
Time after transplantation (days)	-	-	0.174 <sup>a</sup>	-	-	0.175 <sup>a</sup>
Age (years)	-	-	0.893	0.009	0.002-0.017	0.018 <sup>a</sup>
DOAC use	-	-	0.329	0.121	0.021-0.222	0.020 <sup>a</sup>

<sup>a</sup>Variables included in the final model.

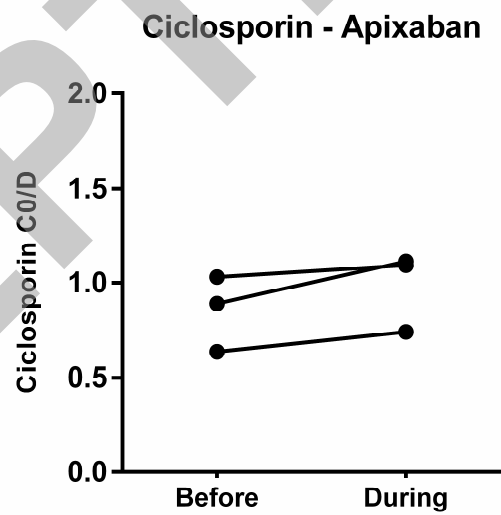
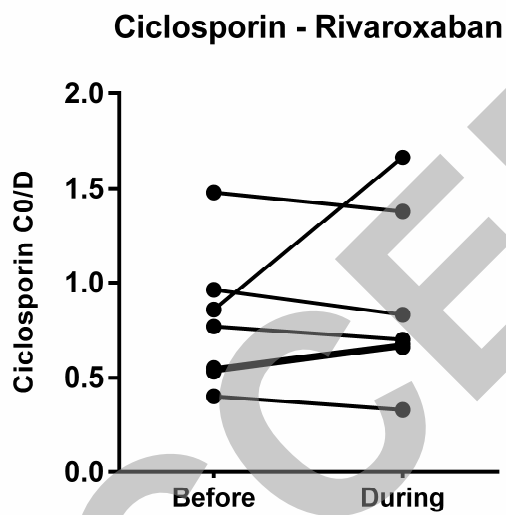
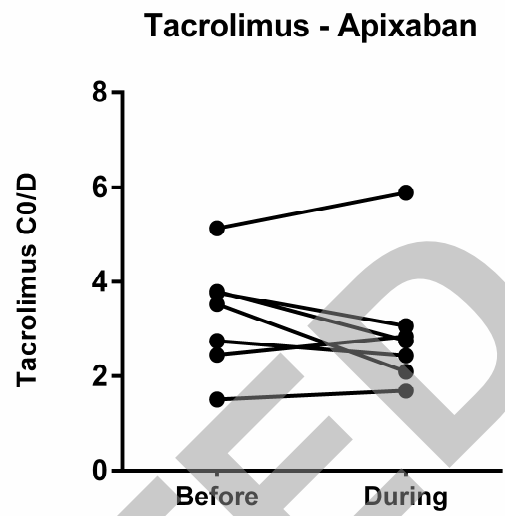
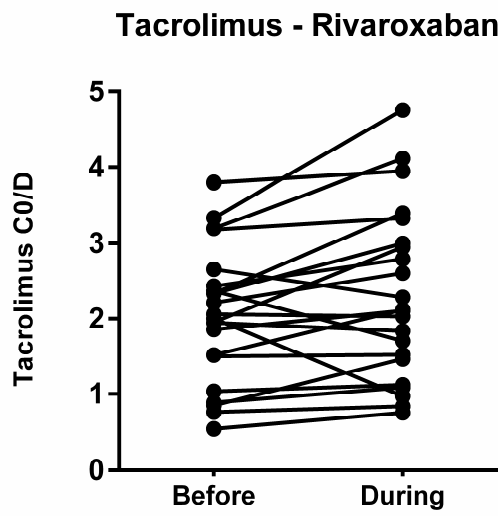
<sup>b</sup>No cases

CI, confidence interval; DOAC, direct oral anticoagulant

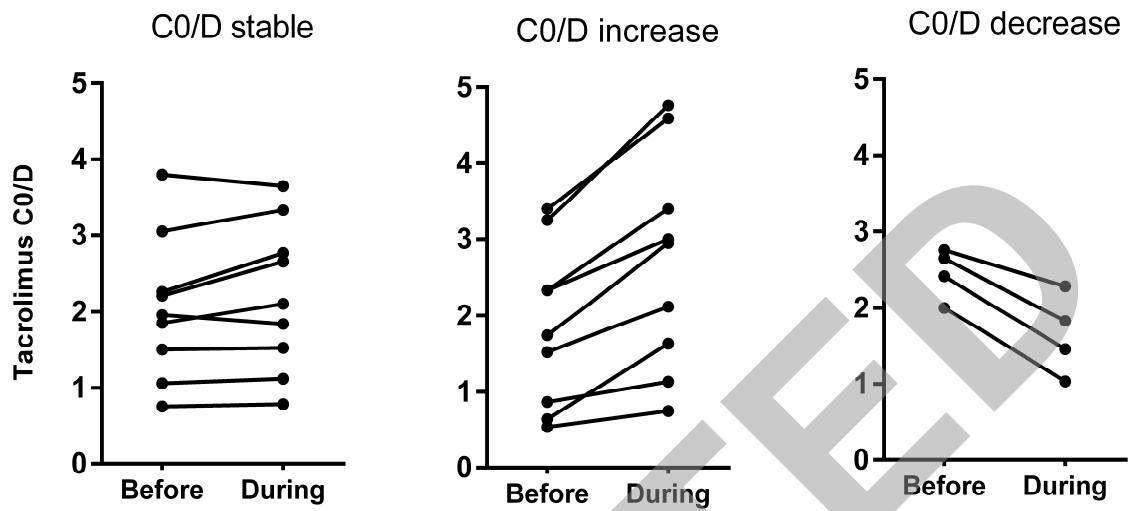
The endpoint of C0/D (dose-corrected trough concentration) is log-transformed. A one-point increase in a predictor value will result in a  $[(e^B)-1] \times 100\%$  increase in C0/D, where B is the estimated effect. For example, tacrolimus C0/D is expected to decrease 0.7% per 1 mg increase in methylprednisolone dose, and DOAC use is associated with a 12.1% increase in ciclosporin C0/D. This method of reporting was chosen because back-transformed effects would relate to absolute (ng/ml/mg) changes in C0/D, which were considered less relevant than relative (%) changes.

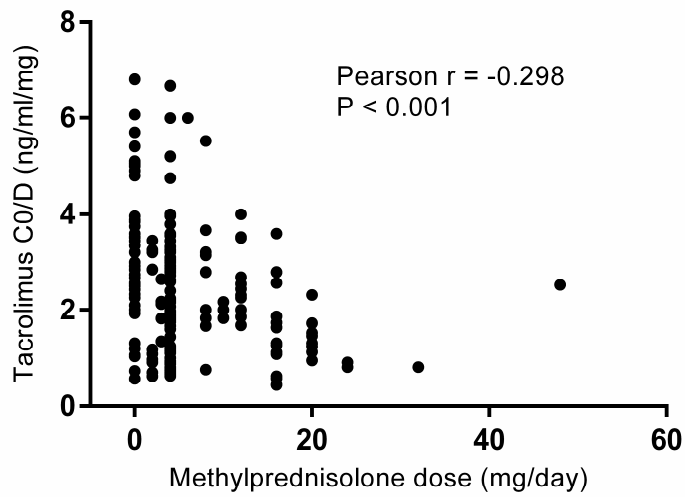






# Tacrolimus - Rivaroxaban





ACCEPTED